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Loss of HS2ST1 cooperates with MAPK inhibition to impair growth of mesenchymal KRAS mutant NSCLC

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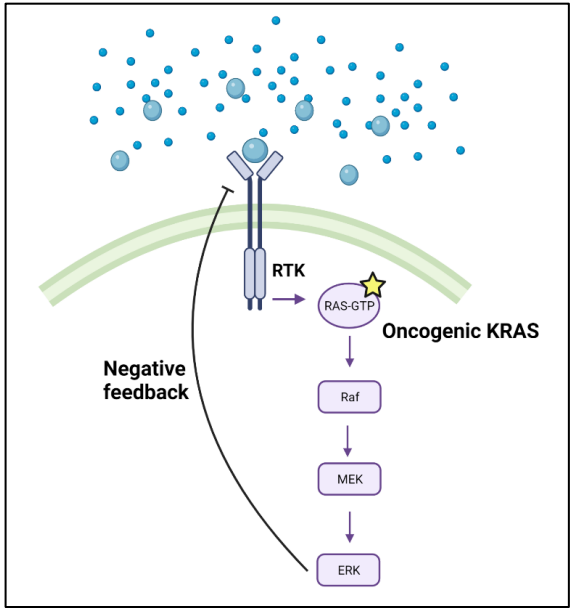
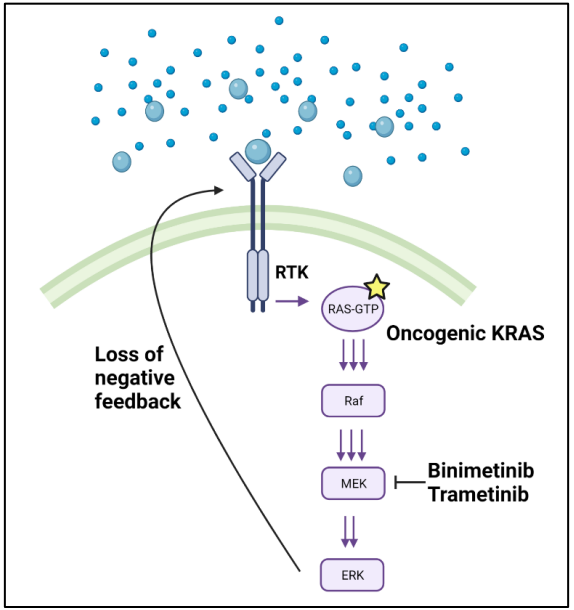
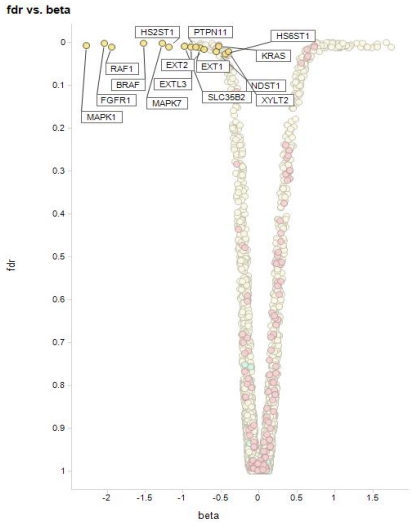
MAPK pathway inhibition blocks negative feedback of MAPK loop leading to intrinsic resistance



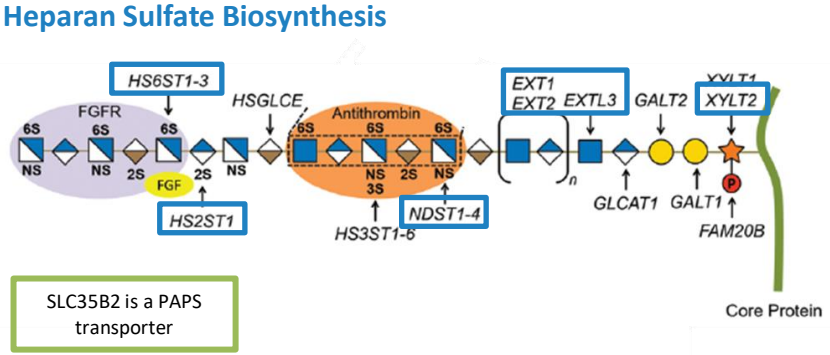


- Inhibition of the negative feedback loop of the MAPK pathway drives upfront resistance to MAPK-targeting monotherapy

Heparan sulfate biosynthesis genes, including HS2ST1, are synthetic lethal with MAPK inhibition

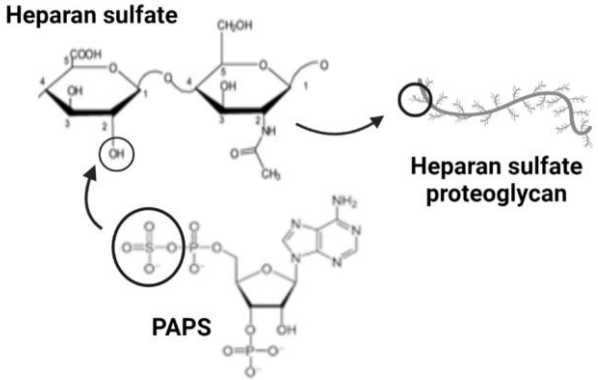


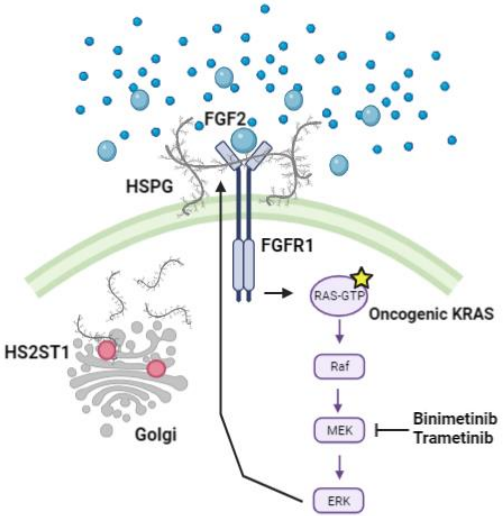
A549 cells with trametinib and CRISPR druggable genome library



- The screen identified genes that are known to cooperate with MAPK inhibition in KRAS-mutant cancer
- The screen identified a novel synthetic lethal pathway in heparan sulfate biosynthesis genes, including HS2ST1

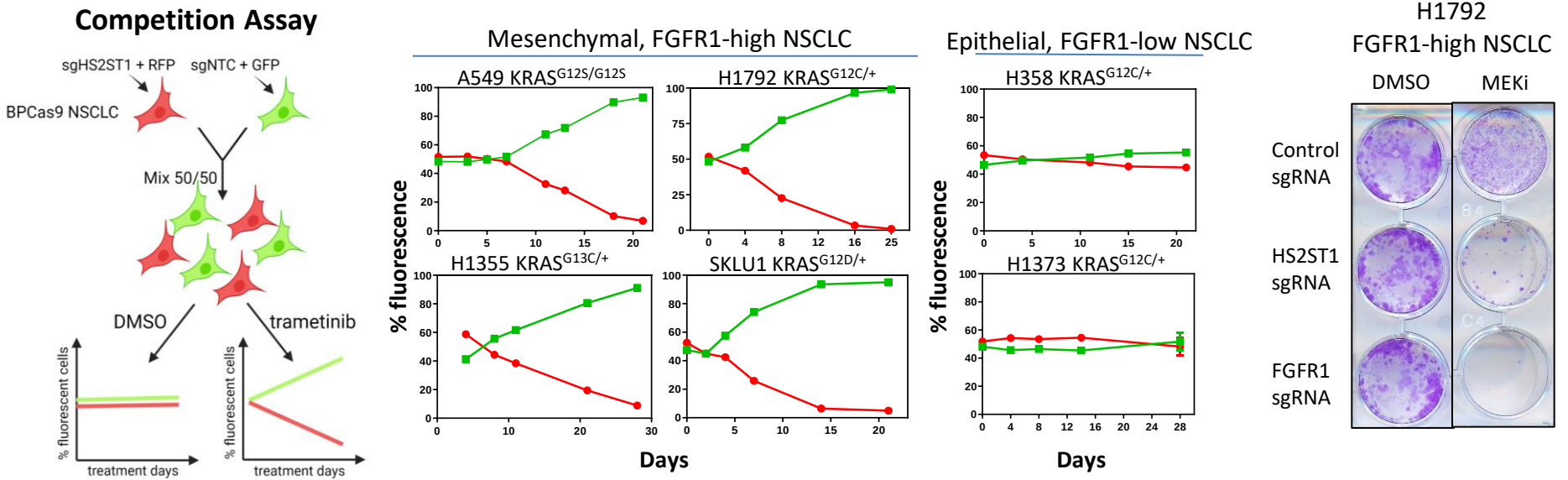
HS2ST1 modifies heparan sulfate proteoglycans to enable activation of FGFR1 by FGF2





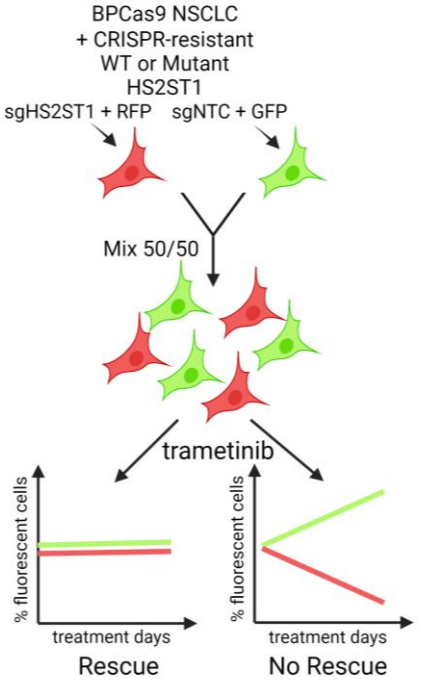
- HS2ST1 modifies heparan sulfate proteoglycans to drive FGF2-FGFR1 interaction
- Suggests that HS2ST1 is required for mediating RTK signaling downstream of MAPK pathway feedback
- HS2ST1 blockade could provide a superior therapeutic index than pan FGFR inhibitors currently available

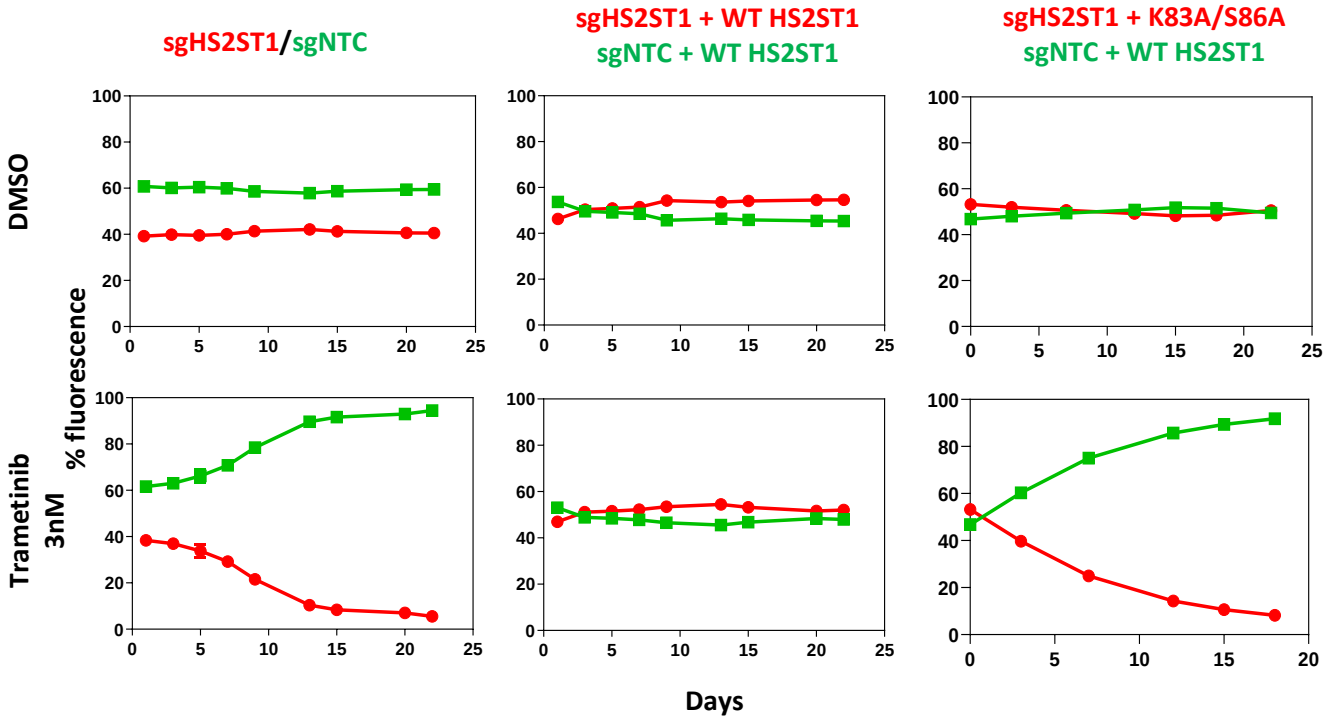
HS2ST1 is synthetic lethal with MEK inhibitors in mesenchymal NSCLC



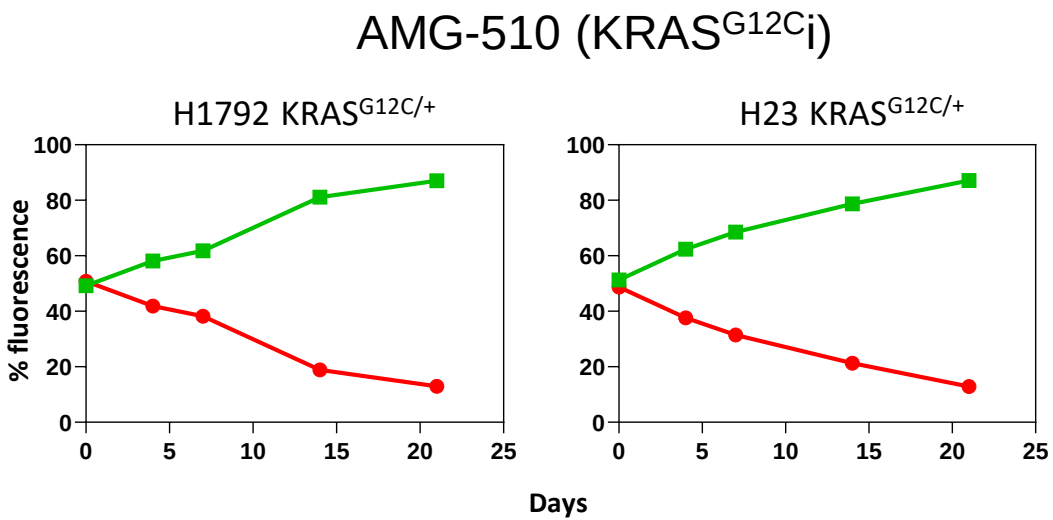
- HS2ST1 knockout cells deplete with trametinib in FGFR1-high NSCLC, and not in FGFR1-low or non exon 2 KRASm NSCLC
- HS2ST1 knockout phenocopies FGFR1 knockout in these NSCLC cell lines

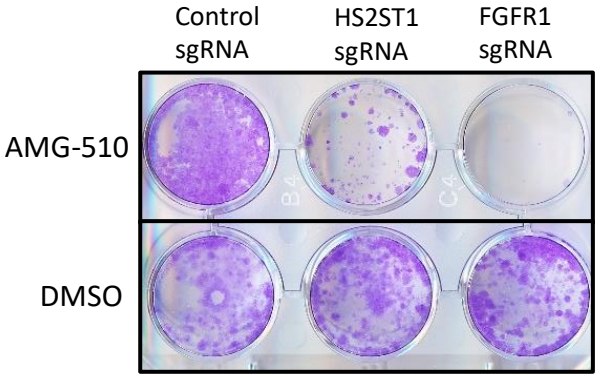
Enzymatic activity of HS2ST1 is required for synthetic lethal activity





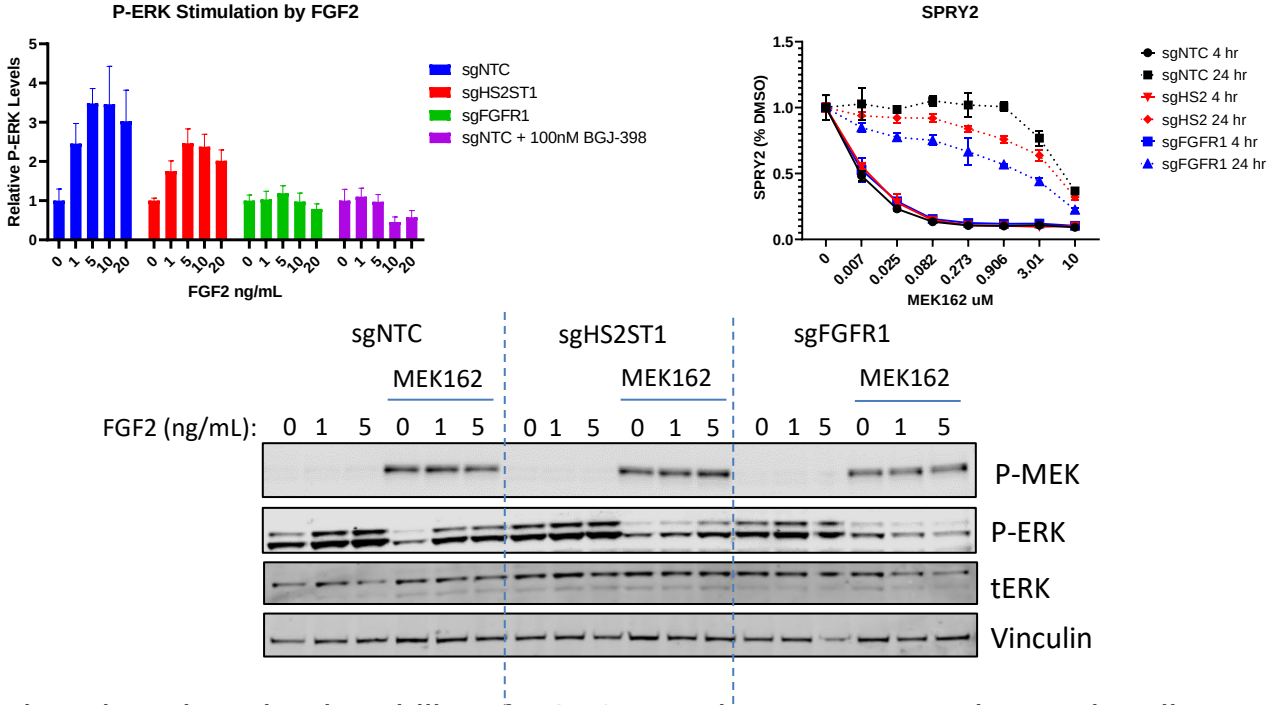
HS2ST1 is also synthetic lethal with KRAS^{G12C}-specific inhibitors





- Inhibition of HS2ST1 enzymatic activity impairs growth of FGFR1-high NSCLC in combination with KRAS or MEK inhibitors

HS2ST1 is required for mediating FGF2-FGFR1 signaling downstream of MEK inhibitor treatment



- HS2ST1 knockout impairs the ability of FGF2 to activate MAPK pathway signaling
- HS2ST1 knockout reduces feedback reactivation of the MAPK pathway downstream of MEKi treatment

Loss of HS2ST1 cooperates with MAPK inhibition to impair growth of mesenchymal KRAS mutant NSCLC

- HS2ST1 and other heparan sulfate biosynthesis genes are novel synthetic lethal targets identified in a CRISPR screen with MEK inhibitor for mesenchymal KRASm NSCLC
- Enzymatic activity of HS2ST1 is required for mediating FGF2-FGFR1 pathway feedback downstream of MAPK inhibition
- HS2ST1 knockout impairs FGF2 signaling in mesenchymal NSCLC, thus blocking a critical node required for MAPK pathway reactivation in these FGFR1-high cells
- HS2ST1 inhibition may provide a novel approach to improve MAPK pathway blockade that may provide an improved therapeutic index over current FGFR inhibitors
- For more information on this CRISPR screening approach, please see poster P183 (Fenoglio et al.)

Acknowledgements

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Contact information

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